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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/867,947	05/29/2001	Alan John Kingsman	674523-2006.1	7750

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/867,947	KINGSMAN ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *23 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,16-18,20-22 and 30-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11, 16-18, 20-22, and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 11, 16, 18, 20-22, and 30 have been amended; and claims 31-33 have been added by the amendment filed August 23, 2004.

The specification has been amended, claims 1-10, 12-15, 19, 23-29 have been canceled, claims 11, 16-18, and 20-22 have been amended, and claim 30 has been added by the amendment dated January 30, 2002.

Applicant's statement with regard to a potential estoppel does not reflect the examiner's position on this issue.

Elected claims 11, 16-18, 20-22, and 30-33 are pending for examination.

In view of applicant's claim amendment, the rejection under 35 USC 112, first paragraph, has been withdrawn.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject

matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

In view of applicant's amendment to the pending claims, the rejection over Olsen is withdrawn by the examiner.

However, applicant's response is not found persuasive for the presently pending claims, which embrace CAEV vector based system, wherein the Tat gene is dispensable.

Claims 16-18, 21, 22, and 30 remain rejected under 35 U.S.C. 102(e) as being anticipated by Harmache (J. of Virology, p. 5445-5454, Vol. 69, 1995).

The claims embrace a CAEV vector based system as claimed in claim 30. Harmache teaches the same the throughout the reference (title, and abstract, and Table

2).

More specifically, the title states:

Three different *tat* gene mutants of an infectious molecular clone of CAEV were used to study their replication aftertransfection or infection of primary goat synovial membrane cells and of blood-derived mononuclear cells or macrophages. Our results showed no difference between replication of the wild type and either the complete *tat* deletion mutant or the *tat* stop point mutant, wherease slower growth kinetics and lower levels of expression of the partial *tat* deletion mutant than of the wild type were obtained in these cells. Quantitative PCR and reverse transcription –PCR analyses of the different steps of a single replicative cycle revealed an identical pattern of retrotranscription, transcription, and viral production, whereas time course analysis demonstrated that the intracellular level of viral genomic RNA was affected by the partial *tat* deletion at later time points. We then compared the infectious properties of the wild-type and *tat* mutant viruses *in vivo* by direct inoculation of proviral DNAs into the joints of goats. All the animal seroconverted between 27 and 70 days postinoculation. Moreover, were were able to isolate *tat* mutant CAEV from blood-derived macrophages that was still able to infect synovial membrane cells *in vitro.* **This study clearly demonstrates that the *tat* gene of CAEV is dispensible for viral replication *in vitro* and *in vivo*** [emphasis added].

Thus, Harmache anticipates the claims.

Applicant's response (page 5) has been considered but is not found persuasive. More specifically and notwithstanding the evidentiary support as set forth above,

Applicant states that since GSM cells were non-permissive to CAEV virus replication, as indicated on page 5452, 2nd column, applicant then extrapolates that an ordinary skilled artisan would understand that Tat has an essential function on replication in certain cells. This assertion was in no way supported by the disclosure of Harmanche. As applicant is aware of, and as evidenced by the totality of the prior art of record, the level of one of ordinary skill in the art is relatively high at the time of filing. As such, the fact that GSM cells are non-permissive to CAEV replication and production does not necessarily mean that *tat* is required or necessary in GSM cells, nor does it necessarily mean that the so-called dispensability of Tat is highly dependent on cell type, origin, and differentiation and activation state. Should a person of ordinary skill in the art look carefully at the total disclosure of Harmache, particularly the figures and tables and supporting conclusions of Harmache, one like Harmache would reasonably conclude that **the *tat* gene of CAEV is dispensible for viral replication *in vitro* and *in vivo*** [emphasis added]. The evidentiary supports can be extracted at numerous figures and tables and data as disclosed in Harmache. See page 5446 column 1, Fig. 2. With regard to the statement by Hamache on column 2 of page 5452, which simply indicates that GSM cells were non-permissive to CAEV virus replication, the statement does not lend any credible support to demonstrate that the so-called dispensability of Tat is highly dependent on cell type, origin, and differentiation and activation state. In fact and more accurately, Harmache additionally states that the origin, and differentiation and activation state of GSM cells, such as differential expression of cellular factors, such as the AP-1 and Jun proteins, known to be involved in the regulation of visna virus gene

expression, may be responsible for the non-permissibility of GSM cells in promoting CAEV virus replication. This is not the same as an unsubstantiated conclusion, which asserts that "the so-called dispensability of Tat is highly dependent on cell type, origin, and differentiation and activation state". On the contrary to this unsupported conclusion, the totality of the Hamache disclosure, particularly in light of the *in vivo* data, which shows that *tat*- CEAV has conserved its infectious property, as revealed by the seroconversion of the goats (Table 2), and is replication competent, as proven by virus isolation from blood-derived macrophages, does indicate conclusively that *tat* is dispensible for ugulate lentiviruses such as FIV, visna virus, and CAEV. See column 1, first full par. page 5433, page 5445, column 1. Note that assuming for argument, applicant's hypothetical assertion is presumed to be correct, such assertion appears to show that applicant's disclosure, in which relevant factual data with respect to EIAV is provided only, does not appear to reasonably enable the full scope of the presently pending claims. As such and should this prior art rejection be withdrawn subsequently due to this specific assertion, the examiner will have to reassess the new ground of rejection under 35 USC 112, first paragraph.

Claims 16-18, 20-22, and 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harmach taken with Naldini *et al.* (US Pat No. 6,428,953), and Chang (US Pat No. 6,207,455).

To the extent that the claims embrace a non-primate lentiviral CAEV based particle, wherein the particle is employed as a delivery vector for delivering a NOI to a

cell, the following rejection is applicable.

The teaching of Harmanche is applied here as indicated above. Harmache does not teach explicitely that the CAEV vector comprises a NOI and used as a delivery vector. However, Harmanched teaches that the *tat* gene is dispensible during the making or production of the CAEV particles.

However, at the time the invention was made, the concept of making lentiviral vectors as a delivery vector comprising a NOI in the absence of a functional *tat* gene is well-established in the prior art, as exemplified in Naldini and Chang. Both of Naldini (column 9, lines 55-56, for example) and Chang (column 28 through column 29) do teach that as long as a strong heterologous LTR (CMV-IE-LTR) is employed to increase basal promoter activity, lentiviral replication such as HIV replication can be sustained without Tat.

In addition, Chang teaches that "due to the restricted tissue tropism of the native lentiviral env gene, lentiviral vectors were developed that use a pan-tropic envelope gene such as amphotropic MLV env or VSV-Gs.

As such, it would have been obvious for one of ordinary skill in the art to delete the *tat* gene from the CEAV system as described in Harmanche and employ the CEAV based particle as a delivery lentiviral vector comprising a NOI. One of ordinary skill in the art would have motivated to do so because such modifications are routine in the prior art, as disclosed in both Naldini and Chang, and because Chang teaches that a replication defective lentiral vector can be used a delivery vector comprising a NOI. One would have expected that CEAV can be made without the presence of a functional

tat on the basis of the combined teachings provided by the references as a whole. The totality of the prior art of record, as exemplified, does teach generically that lentiviral particles including both primate and CEAV based particles can be made without the presence of a functional *tat.*

It would also have been obvious for one of ordinary skill in the art to replace the env gene function of the CEAV vector particles of the combined cited reference with tthe VSV-G envelope gene. One of ordinary skill in the art would have been motivated to use a pan-tropic envelope gene such as VSV-Gs in order to expand their restricted host cell tropism via pseudotyping with vesicular stomatitis virus G (VSV-G) envelope glycoproteins.

Thus, the claimed invention as a whole was *prima facie* obvious.

Applicant's argument on page 6 is also not found persuasive because the remaining prior art rejection is focused mainly on CEAV viruses, and not HIV viruses. As set forth in Harmanche, the reference clearly indicates that "CAEV" belongs to a lentivirus group distinct from that of a HIV virus. For example, Harmanche teaches on page 5445, column 1 bridging column 2, that the group wherein CAEV viruses belong consists of the Tat proteins of FIV, visna virus, and CAEV, which weakly transactivate their LTRs and do not possess a TAR sequence. Note that the Tat proteins of HIV, SIV, BIV, and EIAV, which strongly transactivate their LTRs upon binding to a TAR target sequence. Note also that the Chang patent is an US issued patent, which does claim –*tat* lentiviral vectors, which includes HIV vectors, and thus, is presumed to be valid. This validity of the issued claims is further supported by the following paragraphs

of Naldini and Chang, respectively:

Thus, vectors containing the above-described alterations at the 5' LTR, 5' vectors, can find use as transfer vectors because of the sequences to enhance expression and in combination with packaging cells that do not express tat.

Such 5' vectors can also carry modifications at the 3' LTR as discussed hereinabove to yield improved transfer vectors which have not only enhanced expression and can be used in packaging cells that do not express tat but can be self-inactivating as well.

Mutant constructs containing both LTR and tat mutations were established. These LTR/tat double mutants were generated using the LTR mutant constructs which exhibited enhanced transcriptional activity after inserting heterologous enhancer elements. The recombinant LTR (CMV-IE-HIV-LTR), which has been shown to exhibit increased basal level of promoter activity, can support HIV-1 replication without Tat (L.-J. Chang and C. Zhang, Virol., 211:157–169 [1995]; D. Robinson et al., Gene Therap., 2:269 278 [1995]).

During the development of the present invention, it was determined that the tat-C mutant is more defective than the tat-A and -B mutants, and the dl.Sp1/CMV tat-B double mutant is more defective than the dl.Sp1/CMV LTR mutant or the dl.Sp1/CMV tat-A double mutant reported previously (L.-J. Chang and C. Zhang, Virol., 211:157–169 [1995]). The dl.Sp1/CMV tat-B double mutant infects human lymphoid cell lines with delayed kinetics and exhibited reduced cytopathic effects.

In addition, this double mutant HIV-1 infected primary human PBLs poorly and replicated in primary macrophage culture with reduced kinetics. Based on these results, these already attenuated HIV-1 constructs, dl.Sp1/CMV tat-B and dl.Sp1/CMV tat-C, were chosen for HIV vector development.

Attenuated LTR/tat Double Mutants.

The examiner would also like to point out that the examiner has not considered applicant's assertion regarding the Chang 's failed production of tat-minus HIV-1 vector production, since no pages and lines are cited to support the assertion, and since the

rejection of the presently pending claims is focused mainly on CEAV lentiviruses, which neither the same as HIV-1 nor similar to that of a primate lentivirus. Furthermore and on the contrary to applicant's assertion, Dull (J. Virology, Vol., 72, 11, pp. 8463-8471, 1998) does teach and provide supporting evidence showing that HIV vectors can be routinely produced, whether or not they were produced in the presence of Tat (see entire disclosure, abstract, for example).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11, 16-18, 20-22, and 30-33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 6,312,682 B1 in view of Olsen. Although the conflicting claims are not identical, they are not patentably distinct from each other because

Both set of claims embrace a non-primate lentiviral particle comprising a non-primate lentiviral genome, which comprises regulatory sequences of both the 5' LTR and 3' LTR, a packaging sequence comprising a nucleic acid coding for a functional *gag* protein, and a NOI coding sequence, wherein the genome lacks the *tat* gene. While the patent claims do not teach explicitly that the lentiviral particle includes but includes the leader sequences between the end of the 5' LTR and the ATG of *gag,* such is well-known in the prior art, as exemplified by Figure 1 of the patent and the disclosure of Olsen. Claim 69, for example, claims a pseudotyped VSV-G based lentiviral vector. Further, while the patent claims are silent about EIAV, such would constitute as an obvious variant of the patent claims, since the prior art as exemplified by Olsen teaches a vector production system, EIAV particles, and a delivery system, each of which comprises an EIAV vector that contains at least one defect in at least one encoding an EIAV structural protein, an expression cassette having an NOI coding sequence (abstract). Figures 3 and 4 of Olsen also describe an exemplified EIAV vector that can be used in a delivery system comprising a pharmaceutically acceptable carrier, wherein the vector comprises regulatory sequences of both the 5' LTR and 3' LTR, a packaging sequence comprising a nucleic acid coding for a functional *gag* protein. As such, it would have been obvious for one of ordinary skill in the art to apply the teaching of the patent claims to the making and use of any non-primate lentiviral particle such as EIAV. Thus, both sets of patent claims and examined claims are obvious variants of one another.

Applicant's response does not address specifically to the ODP rejection of record. As such, the rejection is maintained.

Applicant's amendment, *e.g.,* addition of claims 31-33, necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

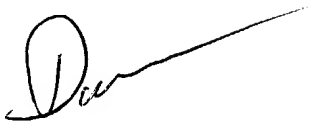
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(571-272-0731)**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson* may be reached at **571-272-0184.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632



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